Potential for using climate forecasts in spatio-temporal prediction of dengue fever incidence in Malaysia

Submitted by

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to the University of Exeter as a thesis for the degree of Doctor of Philosophy in Mathematics, October 2015.

I certify that all material in this thesis which is not my own work has been identified and that no material is included for which a degree has previously been conferred upon me.

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Abstract

Dengue fever is a viral infection transmitted by the bite of female *Aedes aegypti* mosquitoes. It is estimated that nearly 40% of the world's population is now at risk from Dengue in over 100 endemic countries including Malaysia. Several studies in various countries in recent years have identified statistically significant links between Dengue incidence and climatic factors. There has been relatively little work on this issue in Malaysia, particularly on a national scale. This study attempts to fill that gap. The primary research question is 'to what extent can climate variables be used to assist predictions of dengue fever incidence in Malaysia?'. The study proposes a potential framework of modelling spatio-temporal variation in dengue risk on a national scale in Malaysia using both climate and non-climate information.

Early chapters set the scene by discussing Malaysia and Climate in Malaysia and reviewing previous work on dengue fever and dengue fever in Malaysia. Subsequent chapters focus on the analysis and modelling of annual dengue incidence rate (DIR) for the twelve states of Peninsular Malaysia for the period 1991 to 2009 and monthly DIR for the same states in the period 2001 to 2009.

Exploratory analyses are presented which suggest possible relationships between annual and monthly DIR and climate and other factors. The variables that were considered included annual trend, in year seasonal effects, population, population density and lagged dengue incidence rate as well as climate factors such as average rainfall and temperature, number of rainy days, ENSO and lagged values of these

climate variables. Findings include evidence of an increasing annual trend in DIR in all states of Malaysia and a strong in-year seasonal cycle in DIR with possible differences in this cycle in different geographical regions of Malaysia. High population density is found to be positively related to monthly DIR as is the DIR in the immediately preceding months. Relationships between monthly DIR and climate variables are generally quite weak, nevertheless some relationships may be able to be usefully incorporated into predictive models. These include average temperature and rainfall, number of rainy days and ENSO. However lagged values of these variables need to be considered for up to 6 months in the case of ENSO and from 1-3 months in the case of other variables.

These exploratory findings are then more formally investigated using a framework where dengue counts are modelled using a negative binomial generalised linear model (GLM) with a population offset. This is subsequently extended to a negative binomial generalised additive model (GAM) which is able to deal more flexibly with non-linear relationships between the response and certain of the explanatory variables. The model successfully accounts for the large amount of overdispersion found in the observed dengue counts. Results indicated that there are statistically significant relationships with both climate and non-climate covariates using this modelling framework. More specifically, smooth functions of year and month differentiated by geographical areas of the country are significant in the model to allow for seasonality and annual trend. Other significant covariates included were mean rainfall at lag zero month and lag 3 months, mean temperature at lag zero month and lag 1 month, number of rainy days at lag zero month and lag 3 months, sea surface temperature at lag 6 months, interaction between mean temperature at lag 1 month and sea surface temperature at lag 6 months, dengue incidence rate at lag 3 months and population density.

Three final competing models were selected as potential candidates upon which an early warning system for dengue in Malaysia might be able to be developed. The model fits for the whole data set were compared using simulation experiments to allow for both parameter and negative binomial model uncertainty and a single model preferred from the three models was identified. The 'out of sample' predictive performance of this model was then compared and contrasted for different lead times by fitting the model to the first 7 years of the 9 years monthly data set covering 2001-2009 and then analysing predictions for the subsequent 2 years for lead time of 3, 6 12 and 24 months. Again simulation experiments were conducted to allow for both parameter and model uncertainty. Results were mixed. There does seem to be predictive potential for lead times of up to six months from the model in areas outside of the highly urbanised South Western states of Kuala Lumpur and Selangor and such a model may therefore possibly be useful as a basis for developing early warning systems for those areas. However, none of the models developed work well for Kuala Lumpur and Selangor where there are clearly more complex localised influences involved which need further study.

This study is one of the first to look at potential climatic influences on dengue incidence on a nationwide scale in Malaysia. It is also one of the few studies worldwide to explore the use of generalised additive models in the spatio-temporal modelling of dengue incidence. Although, the results of the study show a mixed picture, hopefully the framework developed will be able to be used as a starting point to investigate further if climate information can valuably be incorporated in an early warning system for dengue in Malaysia.

Acknowledgements

My thanks to my supervisor Professor Trevor Bailey for his support and guidance through my PhD journey in CEMPS at the University of Exeter. Thanks also to Professor David Stephenson and Dr Christopher Ferro as, respectively, my second supervisor and postgraduate mentor in CEMPS. Special thanks to all Exeter Climate System academics and administrative support staff who helped me in various ways including Dr Catherine, Dr Rachel, Dr Alemtsehai, Dr Theo, Dr Stan and Dr Yuwei. Lastly, to all friends - Dr Ummu Atiqah, Dr Asma, Dr Alasdair, Dr Lester, Dr Maria, Dr Robin, Siti Hasmah and Noraliza.

Thank you to the Ministry of Education Malaysia (MOE) and Universiti Tun Hussein Onn Malaysia (UTHM) for my financial support in respect of this study. Appreciation to Dr Lokman Hakim, Director of Disease Control Division, for his kind assistance regarding dengue data, also to the Malaysian Meteorological Department (MMD) and the Department of Irrigation and Drainage Malaysia (DIDM) for supplying temperature and rainfall data.

Special thanks to my husband, Yusliandy Yusof, my adorable sons and daughter; Afham Hakim, Ammar Hafiz and Amna Haura for their love and support. Appreciation also to my mother Siti Melia Awang and my late father, Che Him Mamat, for their encouragement in my studies. Lastly, thanks to my family in law and all my brothers and sisters, Mazrah, Zaidi, Al-Zuhari, Azani, Azman, Ariza, Nor-Roshayati, Kamarul Halim, Khairiah Mahayu, Kamarudin and Kamariah, thank you all for your love and your invaluable encouragement.

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Chapter 1

Introduction

This chapter introduces the key motivations behind this study and the primary research aims which are addressed. The focus of the study is on exploring the relationship between climatic variables and the incidence of dengue fever in Malaysia and also the potential for using any such relationships to assist in providing early warning forecasts of dengue epidemics. The chapter starts by outlining the growing need to better understand the risk factors associated with dengue fever, both globally and, more specifically, in the context of Malaysia. It then goes on to specify research aims for the remainder of the thesis and concludes by setting out a structure for the subsequent chapters of the study.

1.1 Motivation

Dengue fever (DF) is a viral infection characterised by sudden high fever, severe headache, rash, muscle and joint pains. The virus is transmitted by the bite of female *Aedes aegypti* mosquitoes and infection rates of dengue can be as high as 90% among those who have not been previously exposed to the virus (Gubler, 1998). Dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) are more serious (and potentially fatal) complications of the disease. Guzman and Kouri

(2002) have reported that nearly 40% of the world's population is now estimated to be at risk from DF in over 100 endemic countries and 500,000 people are estimated to be hospitalised every year with DHF.

The number of dengue cases in Malaysia continues to rise annually and DF is now recognised as a significant public health problem in that country (Smith, 1957; Aziz et al., 2012; Chew et al., 2012). Efforts to reduce the number of dengue cases is now a high priority of various internal and external agencies in Malaysia, not least the Malaysian Ministry of Health which has the main responsibility in addressing the situation. Dengue fever was first reported in Malaysia by Skae (1902), followed by dengue hemorrhagic fever and dengue shock syndrome epidemics in 1962 in Penang, and dengue fever cases first became officially notifiable in 1971 (Rudnick et al., 1965; Poovaneswari, 1993). Now in Malaysia it is the responsibility of all medical practitioners to report every case of dengue fever to the nearest Local Health Office within 24 hours from the time it was diagnosed (Narwani et al., 2005). As the reporting systems have developed, and particularly since 1980, the Malaysian Ministry of Health has recorded continual rising annual cases of dengue to the extent that Ang et al. (2010) recently highlighted dengue fever as an urgent major public health threat in the highly urbanised states of Selangor and Kuala Lumpur.

In general, climate is known to have the potential to influence human health through both direct and indirect mechanisms. The direct mechanisms include, for example, episodes of heat or cold stress and extreme events (drought and flood), while the indirect mechanisms include, for example, the impact of climate anomalies on the risk of vector borne infectious diseases such as malaria and dengue through changing environmental conditions for the vector (Connor et al., 2010). According to Gage et al. (2008), prediction of the relative impact of sustained climate change for vector borne diseases is difficult and will require long-term studies that need to look not only at the effects of climate change but also the contributions of other agents of global change. That said, several studies worldwide have revealed relationships between climatic variables and dengue fever and how these interact with other known risk factors such as socio-economic conditions. Such studies have typically used statistical modelling methods of varying sophistication including time-series analysis, multivariate regression, generalised linear models (GLM), generalised linear mixed models (GLMM), generalised additive models (GAM) or generalised additive mixed models (GAMM). Better understanding of how socio-economic and climatic factors can affect the transmission of dengue fever may help in developing early warning systems (EWS) for epidemics of dengue and so widen the effectiveness of responsive measures (surveillance and prevention). Khun et al. (2005) emphasised the importance of developing systems for early identification for dengue epidemics to help health authorities in surveillance and prevention. To be effective such EWS need to be able to target forecasts geographically within a country into smaller areas such as districts, states or regions (Hu et al., 2012).

In Malaysia, the dengue incidence rate (DIR) in the country as a whole in recent years has fluctuated from as low as 27.5 cases per 100,000 population in 1995 to the high level of 132.5 cases per 100,000 population in 2004 (Kumarasamy, 2006). Epidemics of dengue have occurred roughly every four years with major outbreaks recorded in 1974, 1978, 1982 and 1990 (Lam, 1993b) and with a generally similar pattern with increasing incidence since then. Significant work has been introduced since the 1970s on prevention and control programmes to eliminate the *Aedes* mosquitoes and larval breeding habitats and on public education and law enforcement. However, there have been relatively few modelling studies on the relationship between dengue and climatic and other risk factors in Malaysia as a whole and even less work on the practical development of EWS. That background provides the primary motivation for the work developed throughout the subsequent chapters of this study.

One key challenge in pursuing that agenda is the availability of limited information at the local geographical scale in Malaysia, for example models considered in Racloz et al. (2012) were unable to sufficiently account for the spatio-temporal features of the disease because of the limited geographical resolution of available covariates. However, although there has been little work on dengue EWS in Malaysia, there has been more progress in the neighbour of Malaysia to the south. Dengue fever in Singapore was first recognised as an important public health issue in the early 1960s and *Aedes* control programs have been in place since 1969. Forecasting models of dengue fever have also been developed in Singapore. Ma et al. (2008) carried out a study to look at the association between socio-economic variables and dengue incidence in Singapore for five years from 1998 to 2002 and identified significant association between dengue cases and socio-economic or demographic variables, with areas of higher proportion of disadvantaged residents having more dengue cases. Another more recent study in Singapore used Poisson time series modelling including climate factors such as rainfall and temperature up to 16 weeks or 4 months in advance (Hii et al., 2012). Such studies could be the benchmark for encouraging further research, such as that intended in this study, into the relationship between dengue and climatic variables and other risk factors in Malaysia and the potential for developing EWS for dengue based upon such relationships.

Having established that basic motivation, it is perhaps useful at this point to provide more specific detail on some of the issues so far raised; firstly, in relation to dengue on the world stage and, secondly, in the specific context of Malaysia.

As said previously, dengue fever is a vector borne viral infection transmitted by the bite of female *Aedes aegypti* mosquitoes. The number of dengue cases has increased dramatically around the world in recent years due to the absence of vaccines and drugs (WHO, 2012b). The illness is caused by one of four strains of the dengue virus (DENV-1 to DENV-4). All four strains leave multiple symptoms including headache, rashes and increased body temperature. Infection and recovery from one strain of the virus can lead to immunity from that particular strain and that issue complicates the modelling of the disease because information on the serotype of infections is rarely available on any wide scale.

Potential individual and ecological risk factors for the disease are varied including both socio-economic and environmental conditions. On the socio-economic front factors such as age, income, population density, sanitation, drainage and water supply are potentially important. Amongst the environmental considerations, dengue fever is strongly believed to be influenced by climate variability in temperature and precipitation. One useful related measure is also what is commonly referred to as the 'El Niño Southern Oscillation' (ENSO) which refers to variations in sea surface temperature (SST) of the tropical eastern Pacific Ocean and in air surface pressure in the tropical western Pacific. ENSO, or equivalently the Oceanic Niño Index (ONI) has three different levels; El Niño, Neutral and La Niña. ONI is a global set of anomalies, and is a useful tool to define patterns of climate change. The most heavy and strong ENSO was reported to occur in the years 1997 to 1998. This El Niño was associated with disasters such as drought, flooding and forest fires around the world (Mark, 2005). Understanding links between ENSO and infectious diseases, particularly those transmitted by insects such as dengue, could provide improved long range forecasting of an epidemic or epizootic (Anyamba et al., 2006). The extent to which ENSO can be linked to epidemics of dengue is still not clear, but there are strong recommendations that it could be investigated in future epidemic forecasting for public health preparedness (Mathuros et al., 2009).

Studies associating ENSO and other climatic variables to dengue are reviewed in detail in a later chapter of this study; however it is worth making some brief preliminary reference to a selection of some of those here. Studies in Singapore close to Malaysia have been referenced earlier. Farther afield, in Venezuela, Aura and Alfonso (2010) found a significant association between high dengue incidence and lower values of ONI, but lower dengue incidence with higher value of ONI. Meanwhile, in Puerto Rico, Jury (2008) and Earnest et al. (2012b) concluded that the variability of dengue cases was positively related to temperature but weakly associated with local rainfall and ENSO. Hurtado-Diaz et al. (2007) reported every degree increase in SST leading to a 46% increase in dengue cases in San Andre's Tuxtla and 42% in Veracruz for 16 and 20 weeks respectively. Adriana et al. (2012) used Poisson and Negative Binomial GLMs to investigate the effect of seasonal factors and the relationship of climatic variables to dengue counts in Rio de Janeiro in Brazil. The results indicated significant relationships with the minimum temperature and precipitation at lag one month before, with a 1 °C increase in a month's minimum temperature leading to a 45% increased in dengue cases in the following month and a 10-millimeter increase in precipitation leading to a 6% increase in dengue in the following month. Other research in the South East of Brazil (Lowe et al., 2013) used Negative Binomial generalised linear mixed models (GLMM) to relate monthly dengue incidence to climate and non-climate covariates. Their results provided probabilistic predictions of future epidemics of dengue several months ahead and the general modelling framework used could apply to other areas of Brazil and other climate sensitive diseases.

One issue which these studies perhaps emphasise is that whilst there is broad agreement that climatic factors do influence variability in dengue incidence, there is no clear consensus as to the degree of such effects or indeed, in some cases, their direction. How climate contributes to increase or decrease the incidence of vector borne diseases in human populations will depend on local climatic conditions and local non-climatic epidemiologic and ecologic factors (Patz and Olson, 2006). In other words, effects are geographically dependent upon the region of the world in question and are confounded with other non-climatic influences in ways which are possibly also geographically specific. It is clear therefore that one cannot necessarily transfer results from elsewhere in the world directly into the Malaysian context. Rather there is a requirement to explore from scratch climatic and other relationships with dengue in the specific Malaysian context if progress is to be made towards developing dengue EWS in Malaysia.

Turning briefly to that Malaysian context (a topic which is picked up in more detail in a subsequent chapter), there are factors which have been suggested globally as encouraging dengue spread which particularly pertain in that country, such as rapid and relatively unorganised urbanisation and high rates of population growth. The rise in global commerce and tourism, global warming and changes in public health policy could be important factors too (Gubler, 1998). Developing economies such as Malaysia are also often criticised for poor construction planning which then causes floods or droughts through failure to consider climate information adequately.

Studies to assess the level of knowledge, attitude and practices in relation to dengue in Malaysia have been conducted in 2003 and 2006 by Hairi et al. (2003) and Wan Rozita et al. (2006). In such studies the aims are to evaluate dengue control through increasing the health promotion activities and exposure of communities to educational campaigns. Results obtained were mixed but generally not very encouraging. Meanwhile, Shekhar and Huat (1992) have highlighted major weaknesses of current epidemiological research on dengue in Malaysia which include the inadequacy of data and lack of sound statistical methods. They considered available data used so far to be too restricted, collected using methods that are not clearly described, and which lack scientific validity. The public health sector at the international level has recognised geographic information systems (GIS)[1] as a new technology which has an ability to change the health of societies and contribute to public health policy investigation, development and execution. The WHO has reported that GIS are potentially valuable tools in data compilation and presentation especially for environmental data linked to health services. In Malaysia, this has been explored in relation to dengue by Shaharudin et al. (2002) with results showing no significant difference in the geographical distribution of dengue cases between 1999 and 2000.

As regards the few studies more directly relevant to this study, Lam (1993b) believed that it is possible to predict the severity of a dengue epidemic by the strain of the circulating serotype, but Chew et al. (2012) makes it clear that the situation in Malaysia is complex – although his study showed the predominance of dengue virus in the capital city of Malaysia (Kuala Lumpur) was DENV-4, it was also the case that all four dengue serotypes were in circulation. Ibrahim et al. (2011) used five years data of dengue (2007-2011) to simulate a dynamic system to predict the spread of dengue outbreak in Hulu Langat, Selangor, Malaysia and the results showed that mean temperature, total amount of rainfall and the total of dengue cases in the previous period were highly significant in predicting the possibility of a dengue outbreak.

[1]http://www.gis.com/

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